PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
RG/G -33668A/LEK		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/002108	28.02.2005	01.03.2004

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/4184 A61K31/695 A61K9/28 C07D403/10

Applicant
LEK PHARMACEUTICALS D.D. et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15.12.2005	21.07.2006

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Kardas-Llorens, E

Telephone No. +49 89 2399-8652

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP2005/002108

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-15 as originally filed

Claims, Numbers

1-18 received on 15.12.2005 with letter of 30.11.2005

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-18
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-18
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-18
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 03/048135 A (TEVA PHARMACEUTICAL INDUSTRIES LTD; TEVA PHARMACEUTICALS USA, INC; DOL) 12 June 2003 (2003-06-12) cited in the application

D2: WO 95/17396 A (MERCK & CO., INC; E.I. DU PONT DE NEMOURS AND COMPAGNY; THE DUPONT MER) 29 June 1995 (1995-06-29)

D3: US-A-5 225 202 (HODGES ET AL) 6 July 1993 (1993-07-06)

D4: US-A-5 962 500 (EIDE ET AL) 5 October 1999 (1999-10-05)

Novelty:
A composition comprising a selected stabilizing substance in a selected amount as claimed in claims 1 and 3, their use (claims 11 and 12) and a method of stabilizing an active by using specific substances (claims 13, 14 and 17, 18), are not disclosed in any one document cited in the search report.
Thus, the subject-matter of claims 1-18 is new (Article 33(2) PCT).

Inventive Step:
The problem to be solved by the present invention may be regarded as to prevent the conversion of the active pharmaceutical ingredient to other polymorph forms which results in degradation or interconversion of the active ingredients.
The solution to this problem proposed in claims 1, 3, 13, 14, 17 and 18 of the present application is considered as involving an inventive step (Article 33(3) PCT), since none of the above cited documents hint to the present solution of the above problem by stabilizing the active ingredient by the selected stabilizing substances.
Comparative stability testing in the present description demonstrates the desired effects.

Certain observations on the international application

-The description is not adapted to the present claims.
-The use of trademarks in claims 9 and 10 is not in accordance with Art. 6 PCT (see Guidelines C III, 4.5b)

1. A pharmaceutical composition comprising an active pharmaceutical ingredient in a first polymorph form susceptible to degradation or interconversion into one or more other polymorph forms, and further comprising a stabilizing substance selected from the group consisting of colloidal silicon dioxide, finely divided silicon dioxide, silicified microcrystalline cellulose, magnesium oxide, and polyethylene glycol, present in amount from about 1 % to about 10% by weight of the composition, and optionally one or more pharmaceutically acceptable excipients.

2. A pharmaceutical composition according to claim 1 wherein said stabilizing substance is selected from finely divided anhydrous silicon dioxide or colloidal silicon dioxide .

3. A pharmaceutical composition comprising an active pharmaceutical ingredient, which is the potassium salt of losartan, in a first polymorph form susceptible to degradation or interconversion into one or more other polymorph forms, and further comprising silicon dioxide, present in amount from about 1 % to about 10% by weight of the composition, and optionally one or more pharmaceutically acceptable excipients.

4. A pharmaceutical composition according to any of the claims 1 to 3 wherein said active ingredient in a first polymorph form is the potassium salt of losartan in amorphous form.

5. A pharmaceutical composition according to any of the claims 1 to 3 wherein said active ingredient in a first polymorph form is the potassium salt of losartan in the polymorph form exhibiting its strongest diffractions in a powder X-ray diffractogram at around 2Θ = 6.9, 13.8, 20.6, 24.0, 24.8, 28.7 and 29,2°.

6. A pharmaceutical composition according to any preceding claim which is in the form of a coated tablet.

7. A pharmaceutical composition according to any preceding claim characterized in that it is coated with a film coating comprising stearic acid or ethylcellulose in an amount of from about 0.1% to about 1.7% by weight of the pharmaceutical composition.

8. A pharmaceutical composition according to any preceding claim which is a finished dosage form comprising a finely divided silicon dioxide.

9. A pharmaceutical composition according to claim 8 wherein said finely divided silicon dioxide is Syloid™.

10. A pharmaceutical composition according to claim 9 comprising from about 3% to about 10% by weight of the composition of finely divided silicon dioxide which is a Syloid™.

11. Use of a composition according to any any of the claims 1 to 7 for the manufacturing of a medicament.

12. Use of a composition according to any of the claims 1 to 7 for the manufacturing of a medicament for treating hypertension and/or chronic renal failure.

13. A method of stabilization of a bulk active pharmaceutical ingredient in a first polymorph form susceptible to environmental influences comprising adding colloidal silicon dioxide, finely divided silicon dioxide, silicified microcrystalline cellulose, magnesium oxide or polyethylene glycol to said active pharmaceutical ingredient

14. A method of stabilization within a pharmaceutical composition of an active pharmaceutical ingredient in a first polymorph form susceptible to environmental influences therein contained comprising adding silicon dioxide, to said active pharmaceutical ingredient in amount from about 1 % to about 10% by weight of the composition.

15. A method of stabilization according to any of the previous 2 claims where the environmental influences cause conversion to another polymorph form.

16. A method of stabilization of an active pharmaceutical ingredient according to any of the previous 3 claims where the active pharmaceutical ingredient is potassium salt of losartan.

17. Use of finely divided silicon dioxide, for the stabilization of an active pharmaceutical ingredient which exists in a first polymorph form to prevent the conversion of the active pharmaceutical ingredient to other polymorph forms.

18. Use of finely divided silicon dioxide, present in amount of about 1 % to about 33% by weight relative to the active pharmaceutical ingredient, for the stabilization of an active pharmaceutical ingredient which exists in a first polymorph form to prevent the conversion of the active pharmaceutical ingredient to other polymorph forms.